REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-3, 5-11 and 13-18 are in the case.

I. CLAIM OBJECTIONS

Claims 5-12 have been objected to under 37 CFR 1.75(c) as allegedly improper because of multiple dependencies. In response, claim 3 has been amended to be dependent only on claim 1, thereby rendering the remaining dependent claims properly multiply dependent. Withdrawal of this objection is now respectfully requested.

II. THE ANTICIPATION REJECTION

Claim 4 stands rejected under 35 U.S.C. §102(b) as allegedly anticipated by Latouche et al. In response, and without conceding to the merit of this rejection, claim 4 has been cancelled without prejudice. Withdrawal of the outstanding anticipation rejection is accordingly respectfully requested.

III. THE OBVIOUSNESS REJECTIONS

Claims 1, 3 and 4 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Latouche et al in combination with U.S. Patent 5,268,371 to Mauclaire et al. Claims 1-4 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 4,992,257 to Bonnet et al in combination with Latouche et al and Mauclaire et al and further in view of Westerman et al.

As noted above, claim 4 has been canceled without prejudice. The obviousness rejections pertaining to claim 4 have accordingly been rendered moot. The rejections of claims 1-3 are respectfully traversed.

The present invention as claimed in claim 1 is directed to a compound linked to an antibody directed against a cell surface antigen of cancer or other diseased cells. The compound has a ring structure of formula VIII as set forth in claim 1, representing a porphyrin, chlorin or bacteriochlorin/isobacteriochlorin ring, in any of its iminonitrogen tautomeric forms. The ring carries four aromatic substituents which themselves each carry one or more hydroxyl groups, one or more of which hydroxyl groups are linked to the antibody. New dependent claims 13-17 are directed to optional features removed form earlier dependent claims. New independent claim 18 combines claims 1 and 3. No new matter is entered.

At the outset it is noted that the present inventors were the first to effectively couple a monoclonal antibody to a porphyrin, to produce a conjugate which is optimal with respect to stability, binding affinity and photochemical properties, and which was capable of selective tumor targeting *in vivo*. This was the first time that such effective conjugates had been produced in the art. The inventors carefully controlled the conjugation conditions and employed a carboxymethylene linker moiety activated by a trifluorophenyl (TFP) group. In this way, it was possible to produce one TFP group per porphyrin ring and thereby avoid the occurrence of cross-linking.

Turning to the cited art, Latouche relates to labelling of a porphyrin with radionucleides, such as ^{64}Cu and ^{67}Cu. Although Latouche proposes to couple porphyrins with antibodies, this is not actually carried out or reported by Latouche. In

fact, the last sentence on page 1666 indicates that the authors were "presently **attempting** to link covalently these substituted porphyrins to monoclonal antibodies, and testing their stability towards demetallation processes." (emphasis added). It is clear therefore that linking had not actually been achieved by Latouche. One of ordinary skill would not therefore have been motivated to arrive at the invention of present claim 1 based on Latouche.

Mauclaire does not cure the deficiencies of Latouche. At column 6, line 35, Mauclaire discloses a linker group of the type used in the present invention, but there would have been no motivation to combine this disclosure with Latouche since the person of ordinary skill would have had no expectation of success, as Latouche had not actually achieved any coupling of antibodies with porphyrins. Mauclaire relates to hydrosoluble porphyrin derivatives, and discusses coupling to biologically active molecules including MAbs by alternative routes, although not involving TFP esters. Mauclaire incorporates radioactive metals at high temperature. Example 20 describes the coupling of a porphyrin to an anti-ACE monoclonal antibody. This uses the compound of Example 9 which in turn is based on the compound of Example 6, which employs the 3-nitro-4-fluorophenyl group for coupling to the ACE monoclonal antibody. Thus, in this example, the monoclonal antibody is directly coupled to the phenyl ring, without the intermediary of a carboxymethylene group, in contrast to one of the embodiments of the present invention (see claim 3 and new claim 18).

It is noted that the immunoreactivity of the complex produced in Example 20 of Mauclaire is equal to 45% and there are 10 porphyrins per antibody (Example 20, last sentence). A generally accepted level of immunoreactivity for clinical use is greater

than 70%. The immunoreactivity of the conjugates of the present invention was 93%.

Furthermore, it is indicated in Mauclaire that there are 10 porphyrins per antibody which is to be compared to the present invention which refers to "not more than four porphyrin molecules coupled to the monoclonal antibody" (page 22, beginning of the second paragraph). Furthermore, no *in vivo* experiments are shown in Mauclaire to demonstrate that the conjugate is capable of selective tumor targeting. No photodynamic therapy experiments are provided to demonstrate that the porphyrin retained its photochemical properties. Thus, although Mauclaire proposes a strategy using carboxymethylene linkers, he only exemplified in Example 20 a non-linker conjugate. Moreover, Mauclaire did not show that the conjugates produced are suitable for selective targeting and photodynamic therapy *in vivo*. The immunoreactivity of the Mauclaire conjugate is below acceptable levels in any event.

Based on the above, it is clear that the first obviousness rejection should be withdrawn. Such action is respectfully requested.

Referring to the second obviousness rejection, Bonnett discloses the synthesis of dihydroporphyrins, but otherwise is irrelevant to the presently claimed invention. Bonnett makes no mention of or suggestion of the use of monoclonal antibodies. Indeed, the Examiner admits in the passage bridging pages 4 and 5 of the Action that Bonnett does not teach many of the essential features of the present invention. Mauclaire is not relevant for the reasons discussed above. Westermann describe an old method for coupling porphyrins to a polyethylene glycol (PEG), but there is no disclosure or suggestion of coupling to monoclonal antibodies. The Examiner points to a speculative sentence on page 849, second column, second paragraph, which

indicates that this observation represents "an interesting first step in favour of the strategy of conjugating photosensitising dyes to anti-tumor antibodies". However, this is not a disclosure which would lead one of ordinary skill to the present invention based on the cited art combination.

As further evidence of non-obviousness, it is noted that around the time the present patent application was filed, problems were associated with coupling of photosensitizers to monoclonal antibodies. As a result, coupling of mTHPC to MAbs for therapeutic use *in vivo* was not obvious as of the filing date of the present application, taking into account the state of art conjugation chemistry. In fact, no suitable mTHPC-MAb conjugates were available for *in vivo* photodynamic therapy (PDT).

The problems facing the inventors arose as follows:

(1) *m*THPC lacks functional moieties for coupling to MAbs (*m*THPC is hydrophobic (not water soluble), which does not allow well-controlled conjugation to hydrophilic MAb molecules);

(2) Potential chemical cross-linking of MAbs can occur during conjugation of *m*THPC;

(3) Impairment of MAb integrity, immunoreactivity and pharmacokinetic behavior can occur upon coupling of *m*THPC, due to, e.g., uncontrolled conjugation procedures and photochemical damage;

(4) Impairment of photodynamic properties of *m*THPC, can occur, resulting in impaired therapeutic (PDT) effects.

To deal with (1), the inventors tetracarboxymethylated *m*THPC, followed by esterification of the four carboxylic groups with TFP, to allow subsequent conjugation to

Mabs, (see Figure 1 (Cont i) of the present application). Referring to (2), a problem encountered when using mTHPC-TFP tetra-esters for conjugation to MAbs was the occurrence of cross—linking, which the present inventors avoided by controlled hydrolysis and isolation of mTHPC-TFP mono-esters, (see Figure 1 (Cont i)). Referring to (3), several sources were identified that can cause antibody deterioration upon coupling of *m*THPC, for example, presence of light and oxygen during *m*THPC modification and conjugation, and uncontrolled conjugation conditions leading to inappropriate *m*THPC:MAb molar ratios. Therefore, conjugations were performed in the dark and under a N_2 atmosphere. Conjugation was well controlled by radiolabeling of *m*THPC as well as the MAb with two different iodine isotopes, which allowed simultaneous counting with a gamma-counter (e.g. ^{125}I and ^{131}I). By doing so, the *m*THPC:MAb molar ratio could be well controlled, resulting in optimal photoimmunoconjugates. (Figure 1 (Cont ii)).

It was established that the MAb retained binding activity upon conjugation of *m*THPC, with an immunoreactivity of greater than 93% (p.18, para 3). This is to contrasted with the immunoreactivity of the complex produced in Example 20 of Mauclaire which is 45% (the generally accepted level of immunoreactivity for clinical use is greater than 70%).

Referring to (4), it was established by the present inventors by way of *in vitro* PDT experiments that mTHPC retained photochemical properties. This is described at page 19 last para to page 20; and Fig. 6A & B of the present application.

In summary, it is clear that one of ordinary skill would not have been motivated to arrive at the presently claimed invention based on the combined disclosures relied on

by the Examiner. Absent any such motivation, a *prima facie* case of obviousness has not been generated in this case. Reconsideration and withdrawal of the outstanding obviousness rejections are accordingly respectfully requested.

Favorable action on this application is awaited.

Respectfully submitted,

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